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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/056,343	04/07/1998	UFFE LOEVBORG	3556.224-US	5207

25908 7590 05/09/2003

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	27

DATE MAILED: 05/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Advisory Action	Application No. 09/056,343	Applicant(s) LOEVBORG, UFFE	
	Examiner William W. Moore	Art Unit 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 April 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *87-96*.

   Claim(s) objected to: *54,55,63,64,83, and 84*.

   Claim(s) rejected: *48-53,56-62,65,66,77-82,85 and 86*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *Attachment*

Advisory Action, Attachment for Paragraph 5

Claim Rejections - 35 USC §103

No claims are amended in Applicant's Paper No. 26 filed April 23, 2003, thus it is considered as a Request for Consideration. Applicant's arguments filed April 23, 2003, have been fully considered with respect to the claims 48-50, 56-59, 65 and 66 rejected for reasons of record as anticipated by or, in the alternative, as obvious over the disclosures of Ladner et al., U.S. 5,223,409, but they are not persuasive. Applicant suggests that Ladner et al. "do not disclose or suggest mapping an epitope but does not deny that Ladner et al. had identified variants of regions of the native amino acid sequence of streptokinase, an enzyme that is "antigenic to an undesirable extent", wherein a variant region will lack one at least one epitope that permits the binding of one or more antibodies raised to the native enzyme. While Ladner et al. do not use the term "epitope", the artisan reading their disclosure would recognize that the "antigenic determinants" which Ladner et al. discuss, i.e., the native IPBDs that bind most effectively in their method to a detecting antibody surface, are epitopes. It is clear that Ladner et al. practice a method wherein they modify a nucleotide sequence encoding the native amino acid sequence, a nucleotide sequence comprised by a vector and expressed by a host cell, at one or more codon positions of the medicinally active streptokinase polypeptide to produce a variant regions of streptokinase that will inherently have reduced allergenicity, thus the artisan would be aware, upon reading the disclosure of Ladner et al. that their method inherently produces a map of streptokinase's antigenic epitopes. Ladner et al. need not point out which are the changes in the native amino acid sequence regions that reduce or abolish recognition by antibodies raised to streptokinase because amino acid sequences of the encoded non-binding variant regions can be deduced and compared to the native amino acid sequence to identify the native epitope the antibody had recognized. Insofar as claims

48 48-50, 56-59, 65, 66, 77-79, 85-89, 95 and 96 do not require that an IgE response to the altered, epitope-reduced, enzyme be reduced to render it less allergenic in animals, the method of Ladner et al. inherently anticipates the claimed method "comprising" the recited steps (a) and (b). Applicant argues limitations absent from the claims in asserting that the change of a single amino acid in a variant sequence relative to the corresponding native region can neither constitute an abolition of an epitope nor define the epitope abolished where no claim requires that a dipeptide, tripeptide, or larger, region constitute the epitope identified by the method. Applicant further argues limitations absent from the claims in asserting that Ladner et al. must disclose a method that produces an enzymatically functional streptokinase because the rejected claims do not require that any enzyme maintain its native degree of functionality, either in substrate recognition or in reaction velocity. The rejection of record is maintained.

Similarly, Applicant's arguments filed April 23, 2003, have been fully considered with respect to the claims 77-79, 85 and 86 rejected for reasons of record as anticipated by or, in the alternative, as obvious over the disclosures of Ladner et al., U.S. 5,223,409, but they are not persuasive. The preamble of claim 77 also recites "comprising", thus permits the steps (a)-(d) to be taken in any order and to include other steps. Step (b) of the claim then relegates the antibodies of step (b) to an optional, unnecessary status, in reciting, in the disjunctive, "mapping . . . by testing the antibodies towards the reference protein or the variants thereof". Where use of the antibodies of step (b) raised to variants of the reference protein are optional, and can be replaced by use of the antibodies of step (b) raised to the reference protein itself, the method described is inherently the method disclosed by Ladner et al. Such is not the case with method of claims 87-96 where, although antibodies to the reference protein are generated, the antibodies must be separately incubated with both the reference protein and a variant, or with two variants, in

order to select less immunogenic variants. This process is neither inherent in the disclosure of Ladner et al. nor suggested by the teachings of Ladner et al., thus claims 87-96 are no longer subject to the rejection of record. The rejection of record is maintained.

Claim Rejections - 35 USC §103

Applicant's arguments filed April 23, 2003, have been fully considered with respect to the rejections of record of claims 51-53, 60-62 and 80-82 as obvious over the disclosures of Ladner et al. taken in view of the teachings of view of either Zacharaiae et al. or Arlian et al., but they are not persuasive. Applicant suggests that the teachings of Zacharaiae et al. or Arlian et al. need to include a reference to the method of Ladner et al. but both were cited to demonstrate the motivation extant at the time the invention was made to apply a method such as that of Ladner et al. to reduce allergenicity and amino acid sequences of the detergent proteases Alcalase® and Esperase® taught by Zacharaiae et al. to cause IgE antibody-mediated sensitization in persons, resulting in chronic, symptoms of respiratory irritation, coughing, shortness of breath, and chest tightening serine proteases and the amino acid sequences of the detergent proteases Alcalase® and Esperase® taught by Arlian et al. to cause respiratory allergy and to exhibit specific, electropositive antigens binding significant levels of human IgE antibodies as demonstrated by crossed immunoelectrophoresis. Applicant does not argue that either of these prior art teachings would have failed to motivate one of ordinary skill in the art at the time the invention was made to extend the method of Ladner et al. to reducing the immunogenicity of these industrial enzymes, thus the rejection of record is sustained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final

communications. The examiner's direct FAX telephone number is 703.746.3169. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

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William W. Moore
May 5, 2003

CHARLES L. PATTERSON, JR.
PRIMARY EXAMINER
GROUP 1800